all or some of the positive controls, negative controls, reagents, primers, sequencing markers, and probes for determining the presence or absence of a tandemly repeated 28 base-pair nucleic acid sequence that defines the genomic polymorphism in the 5' UTR of the TS gene.

59. The kit of claim 58 wherein the kit components may be provided in solution or as a liquid dispersion or the like.

60. The kit of claim 58 comprising DNA tandemly repeated sequences that determine the type of genomic polymorphism of the TS gene in Tris-EDTA buffer solution kept at about 4 °C.

REMARKS

Reconsideration of the application in view of the above amendments and the following remarks is respectfully requested.

As an initial matter, Applicants thank the Examiner for her careful reading of the specification. Applicants have canceled claims 1-34 and have added new claims 35-60. Therefore, claims 35-60 are now pending in the application. No new matter has been added by the claim amendment or the new claims. Support for the new claims is found throughout the specification. See, for example, the section entitled "Predictive Medicine and Pharmacogenomics."

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH

The Examiner rejected claims 1-34 under 35 U.S.C. § 112, second paragraph on the grounds that the claims are indefinite for recitation of various terms. Although Applicants believe that claims 1-34 are clear and definite, Applicants have canceled claims 1-34 without prejudice and have added new claims 35-60, which do not contain the objected to terms. Therefore, this rejection has been rendered moot.

Thus, the new claims do not contain the word "effect" or its permutations. Similarly, the new claims do not contain the step of concluding or the terms "certain type", "associating," "appropriate," "preferably" or the relative terms "most," "best," "poorest," and

"less poor." Further, using the Examiner's suggestion the meaning of TS and UTR is recited at the first occurrence of the terms in the claims followed by the abbreviation in parenthesis.

Based on the foregoing, Applicants respectfully request that the claim rejection under 35 U.S.C. § 112, second paragraph be withdrawn.

CLAIM REJECTIONS UNDER 35 U.S.C. § 112, FIRST PARAGRAPH: WRITTEN DESCRIPTION

The Examiner rejected claims 1-30, and 31-33 under 35 U.S.C. § 112, first paragraph on the grounds that the specification does not contain a written description of the invention. Applicants have cancelled claims 1-34, mooting this rejection. Nevertheless, Applicants offer the following arguments to rebut the rejection and to support new claims 35-60.

In general, a written description rejection under § 112, first paragraph should not be made against originally filed claims. As the MPEP notes, there is a strong presumption that an adequate written description of the claimed invention is present when the application is filed. MPEP, 8th Edition, August 2001 at 2100-158 to 159 citing In re Wertheim, 541 F.2d 257, 263 (CCPA 1976). Consequently, rejection of an original claim for lack of written description should be rare. Id.

The Examiner asserts that the written description is inadequate because the specification fails to describe a representative number of species for each genus in the claims because each genus is extremely large and variable in view of the plethora of known cancers, etc. This assertion is not entirely consistent with the law. Even disclosure of a single species may be enough to meet the written description requirement of § 112 - as such there is no requirement that more than one species be disclosed to support a genus. In re Rasmussen, 650 F.2d 1212, 1214 (CCPA 1981). Therefore, the Examiner's assertion is not supported by the law.

To limit Applicants to narrow genera or single species would be patently unjust. Applicants have made a pioneering discovery relating the efficacy of therapeutic regimens for treating a disease in a subject to a genotype of a gene of the subject. In view of the pioneering nature of their discovery, Applicants should be allowed to claim their invention broadly. As it is, Applicants have limited the claims to only one type of disease, i.e., cancer. Any further limitation would be unfair and would stifle innovation.

In any event, Applicants' new claims further limit various genera. Thus, in claim 35, the genus of therapeutic regimens is limited to administration of chemotherapeutic drugs and the genus of cancers is limited to a group of 7 cancers commonly treated with chemotherapeutic drugs. Independent claim 44 is even narrower – it limits the genomic polymorphism to one type of genomic polymorphism, i.e., the disclosed species.

Therefore, Applicants respectfully submit that new claims 35-60 meet the written description requirement and request that they be passed to allowance.

CLAIM REJECTIONS UNDER 35 U.S.C. § 102(b)

The Examiner rejected claims 22-24 under 35 U.S.C. 102(b) as being anticipated by Horie et al. Applicants have cancelled claims 22-24 without prejudice to pursuing these claims in a subsequent application. Therefore, this rejection is now moot.

Nevertheless, Applicants respectfully dispute the propriety of this rejection. Horie et al. is a study of the repeated sequences in the 5'-terminal region of the TS gene using an artificial construct in which a reporter gene is linked to the promoter region of the TS gene. Thus, Horie et al. report the expression activity of this artificial construct and that too based on *in vitro* experiments. Therefore, it is simply improper to assert that Horie et al. show that the level of expression of the TS gene in a subject is correlated with the genomic polymorhphism of the TS gene.

Applicants, on the other hand, have shown that the number of tandemly repeated sequences in the hTS gene affects the level of TS mRNA in tissue, tumoral as well as normal, obtained from human subjects. Thus, using such tissue samples, Applicants have shown, for the first time, that individuals with the L/L genotype had 3.5 times higher TS mRNA levels in tumor tissue and about 2.5 times higher in normal tissue when compared with levels in comparable tissues in individuals with the S/S genotype.

CLAIM REJECTIONS UNDER 35 U.S.C. § 103(a)

The Examiner rejected claims 1-16, claims 17-21, claims 26-30, and claims 32-34 under 35 U.S.C. 103(a) as being unpatentable over Horikoshi et al. (Cancer Res. 52:108-116

(1992)), henceforth referred to herein as Horikoshi, in view f Horie et al. (Cell Struct. Funct. 20:191-197 (1995)), henceforth referred to herein as Horie.

Applicants vigorously dispute this rejection. Horikoshi in combination with Horie does not render the pending claims obvious to one of ordinary skill in the art. As an initial matter, Horikoshi was published in 1992 and Horie was published in 1995. This begs the question that if it was obvious to combine Horikoshi with Horie to produce the instant invention, why was the claimed invention not made (for example, by either Horikoshi or Horie) prior to Applicants.

In any event, Horikoshi cannot be combined with Horie to yield the claimed invention. The Examiner correctly notes that Horikoshi shows that the response of human subjects to TS directed drug therapy is inversely proportional to the level of TS expression. In fact, the specification of the instant application cites prior work, which has shown that the sensitivity or resistance to 5-FU is dependent on levels of TS in tumors. It has been known for some time that the active metabolite of 5-FU binds to TS. Therefore, the higher the level of TS in tumors, the more 5-FU will be used up in binding to TS and the lesser will be the therapeutic benefit of 5-FU.

Applicants have built upon this knowledge by discovering that intracellular and intratumoral TS mRNA levels are correlated with polymorphism in the 5'-UTR of the TS gene. Applicants have combined this discovery with the prior knowledge, i.e., TS gene expression determines the effectiveness of TS directed therapy, to make their pioneering invention wherein polymorphism in the TS gene is used to determine the effectiveness of TS-directed drugs, such as 5-FU.

The knowledge provided by Applicants' discovery is clearly not available in Horikoshi. It is not provided by Horie either. Horie does not and cannot provide the necessary information that must be combined with Horikoshi to produce the instant invention. Horie did not measure intracellular or intratumoral TS levels or TS mRNA levels (Horie did not even study the TS gene *per se*). Therefore, Horie does not provide the necessary basis for correlating intracellular TS gene expression with the 5'-UTR polymorphism in the TS gene. Because Horie is missing this critical information, it cannot be the basis for correlating the aforesaid genomic

polymorphism with the efficacy of TS-directed drugs, which is one of the embodiments f Applicants's invention.

Horie, as noted *supra*, merely studied the repeated sequences in the 5'-terminal region of the TS gene using an artificial construct in which a reporter gene is linked to the promoter region of the TS gene. Thus, Horie reports the expression activity of this artificial construct based on *in vitro* experiments. By no means does Horie provide an enabling disclosure that shows that the level of expression of the TS gene in a subject is correlated with the genomic polymorhphism of the TS gene.

Therefore, combining Horie with Horikoshi will not yield the claimed invention. If Horie had measured and correlated intrcellular expression of the TS gene or the TS mRNA level (an indirect measure of gene expression) with the 5'-UTR polymorphism of the TS gene, as Applicants have done, Horie *could have been* combined with Horikoshi to provide the claimed invention. But that is not the case. Therefore, Horie's combination with Horikoshi does not yield the present invention.

Additionally, the Examiner has not met the requisite burden for combining Horikoshi with Horie to reject Applicants' claims under section 103. The U.S. Court of Appeals for the Federal Circuit has held that "[t]he PTO has the burden under section 103 to establish a *prima facie* case of obviousness...It can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988).

The Examiner merely states that it would have been "obvious to one of ordinary skill in the art at the time the invention was made to" to combine Horie with Horkoshi to arrive at the claimed invention. See, for example, Office Action at pp. 6-7 and at p. 8.

Thus, the Examiner does not point to any discernible suggestion in either Horie or Horikoshi that would lead one of ordinary skill in the art to combine the two references. What the Examiner offers is the unsupported assertion that a skilled artisan would have been motivated to combine the two references.

Such an assertion cannot be used to base a finding of obviousness. In re Fine, 837 F. 2d 1071, 1074 (Fed. Cir. 1988). The In re Fine court held that "the Examiner's bald assertion" that substitution of an lement from one reference into another "would have been within the skill of the art" cannot support a finding of obviousness. Id. In the instant case too, the Examiner's statement about combining Horie with Horikoshi is an assertion that is not adequate to support a 103 rejection of Applicant's pending claims.

As discussed above, the combination does not even yield the claimed invention because Horie deals with the behavior of an artificial construct and does not provide an adequate basis for relating the level of expression of the TS gene in a subject with the number of polymorphic repeat sequences in the 5'-UTR of the TS gene.

Case law unequivocally establishes that the motivation to support a combination of references must withstand scrutiny. The Federal Circuit's discussion of this requirement in In re Rouffet, 149 F.3d 1350 (Fed. Cir. 1998) is instructive. There the Court stated:

> "[V]irtually all [inventions] are combinations of old elements." Environmental Designs, Ltd. v. Union Oil Co., 713 F.2d 693, 698, 218 U.S.P.Q. 865, 870 (Fed. Cir. 1983); see also Richdel, Inc. v. Sunspool Corp., 714 F.2d 1573, 1579-80, 219 U.S.P.Q. 8, 12 (Fed. Cir. 1983) ("Most, if not all, inventions are combinations and mostly of old elements."). Therefore an examiner may often find every element of a claimed invention in the prior art. If identification of each claimed element in the prior art were sufficient to negate patentability, very few patents would ever issue. Furthermore, rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention itself as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention. Such an approach would be "an illogical and inappropriate process by which to determine patentability." Sensonics, Inc. v. Aerosonic Corp., 81 F.3d 1566, 1570, 38 U.S.P.Q. 2d 1551, 1554 (Fed. Cir. 1996).
>
> To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a

> motivation to combine the references that create the case of obviousness.

Id. at 1357. The court then noted that the Board had failed to "explain what ***specific*** understanding or technological principle within the knowledge of one of ordinary skills in the art would have suggested the combination." Id. (emphasis added). Finding that the Board had "merely invoked the high level of skill in the . . . art," the court stated:

> If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technical advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, ***the suggestion to combine requirements stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness.***

Id. at 1357-1358 (emphasis added).

Applicants submit that, in the present case, the purported motivation for the cited combination fails to identify the "***specific*** understanding or technological principle within the knowledge of one of ordinary skill in the art" that would lead to the ***specific*** combination on which the rejection is based.[1] Accordingly, the motivation cited by the Examiner is insufficient to support the combination and thus insufficient to support a case of *prima facie* obviousness.

---

[1] See also Ex Parte Clapp, 227 U.S.P.Q. 2.d 1300 (Bd. Pat. App. & Inter. 1985) (When the references do not explicitly suggest combining their teachings, the Examiner must present a convincing line of reasoning to support the rejection.) Thus, a conclusory statement that a reference can be used to improve a certain technique hardly amounts to a reasoned explanation of why it would have been proper to combine that reference with another reference. While the Federal Circuit has held that the recognition of some advantage or expected beneficial result may be a rationale for combining references, that recognition must exist impliedly or explicitly in the references or *be drawn from a convincing line of reasoning based on established scientific*

(Footnote Continued on Next Page.)

Thus, an attempt to combine Horie with Horikoshi by simply assuming that these two references can be combined does not comport with the Federal Circuit's well established rule that the mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. In re Mills, 916 F. 2d 680 (Fed. Cir. 1990). See also In re Laskowski, 871 F.2d 115, 117 (Fed. Cir. 1989)

The Federal Circuit has stated that it is impermissible simply to engage in a hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps. Interconnect Planning Corporation v. Feil, 774 F.2d 1132, 1143 (Fed. Cir. 1985). The references themselves must provide some teaching whereby the applicant's combination would have been obvious. In re Gorman, 933 F.2d 982 (Fed. Cir. 1991). For all of the foregoing reasons, Applicant submits that the attempted combination of references is based on impermissible hindsight reconstruction and the references do not provide any teaching that would have rendered Applicant's invention obvious.

Applicants, therefore, respectfully request the Examiner to withdraw the rejections under 35 U.S.C. § 103.

CONCLUSION

Accordingly, in view of the above amendments and remarks, it is submitted that this application is now ready for allowance. Early notice to this effect is solicited.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned at (213) 680-6678.

(Footnote Continued from Previous Page.)

principles or legal precedent. In re Semaker, 702 F. 2d 989, 994 (Fed. Cir. 1983) (emphasis added).

If an appropriate payment does not accompany or precede this submission, the Commissioner is hereby authorized to charge any required fees, such as under 37 C.F.R. §§ 1.16 or 1.17, including any fees for extension of time or additional claims, or to credit any overpayment, to Deposit Account N . 50-1192.

Dated: February 13, 2002

Respectfully submitted,

McCutchen, Doyle, Brown & Enersen, LLP

By: _____
Rajiv Yadav, Ph.D., Esq.
Registration No. 43,999

McCutchen, Doyle, Brown & Enersen LLP
Three Embarcadero Center, 18th Floor
San Francisco, California 94111
Telephone: (415) 393-2000
Telefax: (415) 393-2286